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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/856,391 | 01/07/2002 | Jamey D. Marth | 19452A-000320US | 7913 |

20350 7590 06/02/2004

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

| EXAMINER | |
|---|---|
| ZARA, JANE J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/856,391 | MARTH ET AL. | |
| | Examiner | Art Unit | |
| | Jane Zara | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *36-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-20-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Office action is in response to the communication filed 4-13-04.

Claims 36-49 are pending in the instant application.

### *Election/Restrictions*

Applicant's election with traverse of Group II in Paper filed 4-13-04 is acknowledged. The traversal is on the ground(s) that Groups II and IX, drawn to methods of modulating an inflammatory response and methods of modulating binding of a first myeloid cell to another cell comprising inhibiting core 2 GlcNAc transferase activity should be encompassed by the same search and should not pose a burden to co-examine. Upon further consideration, Applicants' arguments have been found convincing and both Groups II and IX have been rejoined and claims 36-49 have examined on their merits in the Office action set forth below.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention. The specification and claims do not indicate what distinguishing attributes are concisely shared by members of the genus comprising *compounds that inhibit the activity of core 2 GlcNAc transferase*, or *compounds that modulate the synthesis of a core 2 oligosaccharide* as claimed in the instant application. The specification, claims and prior art do not place any limit on the number, structures or characteristics that fall within this broad genus of compounds (See e.g. Jain et al, Glycobiology 8(7): 707-717, 1998 for an array of possible acceptor substrate analogs for various glycosyl transferases; see also Hindsgaul et al, J. Biol. Chem. 266(25): 17,858-17,862, 1991 for an array of possible sugar nucleotide analogs to test as inhibitors for glycosyl transferases).

The specification teaches generic approaches to inhibiting the target enzyme C2 GlcNAc-T, including agents comprising immunoglobins, suicide substrates, alkylating agents and various substrate analogs. The instant specification also generally discusses sugar nucleotides (e.g. page 21), nucleotides (e.g. page 22), donor and acceptor substrate analogs (e.g. page 22), competing glycosyl transferases and glycosidases (e.g. page 22) as potential agents for inhibiting target C2 GlcNAc-T function, whereby core 2 O-glycans are inhibited. But no common structural attributes concisely identify the members of this broad genus of inhibitors, and the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Because this genus is highly variant, and because the disclosure and art fail to describe the common attributes or characteristics

concisely identifying members of the proposed genus comprising any compounds that modulate the synthesis of a core 2 oligosaccharide or inhibit the activity of a core 2 GlcNAc transferase, and because this genus is highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the very broad genus claimed. Thus, Applicant was not in possession of the claimed genus.

Claims 36-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of systemic C2 GlcNAc $T^{\Delta}$ or conditional C2 GlcNAc $T^{F}$ homozygous mice using Cre-loxP recombination, whereby a deficiency of C2 GlcNAc transferase activity and a deficiency of core 2 O-glycan synthesis were observed in isolated null mouse splenocytes, does not reasonably provide enablement for methods of inhibiting inflammatory responses in a mammal, or for methods of modulating binding of a first myeloid cell to a second myeloid cell or to an endothelial cell in an organism comprising the administration of a compound that modulates the synthesis of a core 2 oligosaccharide or the administration of a compound that inhibits the activity of a core 2 GlcNAc transferase in an organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting an inflammatory response in a mammal and/or modulating binding of a first myeloid cell to either an

endothelial cell or to a second myeloid cell comprising the administration of a compound that inhibits the activity of a core 2 GlcNAc transferase, or that binds to or modulates the synthesis of a core 2 oligosaccharide.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

**The state of the prior art and the predictability or unpredictability of the art.** The following references are cited herein to illustrate the state of the art of glycosyl transferase inhibition or oligosaccharide biosynthesis inhibition. Hindsgaul et al (J. Biol. Chem. 266(25): 17,858-17,862, 1991, esp. at 17,858 and 17,860), in evaluating various oligosaccharide acceptor analogs for glycosyltransferase inhibition, teach that acceptor analogs give varied and unpredictable results in their ability to inhibit intended glycosyl transferase reactions, presumably due to complications involving critical hydrogen bond donor interactions with basic groups on these oligosaccharide biosynthetic enzymes. In addition, Hindsgaul et al state that "[w]hile some such inhibitory analogs have been produced, it seems unlikely that this approach will suffice for the production of glycosyltransferase inhibitors since most sugar nucleotides are donors for ... different glycosyltransferases..." and that "...sugar nucleotide analogs can potentially interfere with biosynthetic pathways involved in the interconversion, metabolism, and transport of sugar nucleotides."

Jain et al (Glycobiology 8(7): 707-717, 1998, esp. at 707, 707)) also teach the unpredictability of synthetic sugar analogs in inhibiting glycosyl transferase

reactions: "Of note, the affinity of selectins for all these synthetic analogs appear to be much poorer than those of the natural glycoconjugate ligands...." These references teach the unpredictability of sugar analogs/acceptor analogs as inhibitors of glycosyl transferase reactions in vitro and the instant disclosure and the art are both silent regarding the ability of such small compounds to specifically inhibit glycosyl transferase reactions in vivo.

**The amount of direction or guidance presented in the specification AND the presence or absence of working examples.** Applicants have not provided guidance in the specification toward a method of inhibiting an inflammatory response in a mammal, or of modulating the binding of a first myeloid cell to either an endothelial cell or a second myeloid cell comprising the administration of any compound that inhibits the activity of a core 2 GlcNAc transferase, or any compound that binds to or modulates the synthesis of core 2 oligosaccharide in an organism. The instant disclosure teaches the production of systemic C2 GlcNAc $T^{\Delta}$, or conditional C2 GlcNAc $T^{F}$, homozygous mice using Cre-loxP recombination. The specification teaches a loss of C2 glcNAc transferase activity, and a deficiency of core 2 O-glycan formation in isolated splenocytes from these null mice, as well as a loss of the B220 epitope in splenocytes in mice lacking C2 GlcNAc transferase activity. The specification also teaches the absence of 1B11 antibody binding to myeloid cells in mice lacking C2 GlcNAc transferase activity. One skilled in the art would not accept on its face the examples given in the specification of generating systemic C2 GlcNAc $T^{\Delta}$ or conditional C2 GlcNAc $T^{F}$ homozygous mice using Cre-loxP

recombination as being correlative or representative of the successful inhibition of an inflammatory response in a mammal or the successful modulation of binding of a first myeloid cell to either an endothelial cell or a second myeloid cell comprising the administration of any compound that inhibits the activity of a core 2 GlcNAc transferase, or that binds to or modulates the synthesis of core 2 oligosaccharide in an organism in view of the lack of guidance in the specification and known unpredictability associated with the inhibition of glycosyl transferases or inhibition of oligosaccharide synthesis in vitro or in vivo comprising the administration of sugar substrate analogs or other potentially inhibitory compounds. The successful generation of null mice is not representative of the ability to successfully target and inhibit C2 GlcNAc transferase in vivo comprising the administration of inhibitors.

**The breadth of the claims and the quantity of experimentation required**. The breadth of the claims is very broad. The claims are drawn to methods of inhibiting an inflammatory response in a mammal and/or modulating binding of a first myeloid cell to either an endothelial cell or to a second myeloid cell comprising the administration of a compound that inhibits the activity of a core 2 GlcNAc transferase, or that binds to or modulates the synthesis of a core 2 oligosaccharide. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring core 2 GlcNAc transferase whereby core 2 glycan biosynthesis is inhibited in vivo and treatment effects are provided for inflammatory responses

in a mammal, and whereby the binding of a first myeloid cell to either an endothelial cell or a second myeloid cell is inhibited in a mammal following administration of such inhibitory compounds. Since the specification fails to provide any particular guidance for the targeting and inhibition of core 2 GlcNAc transferase, or for the modulation of the synthesis of core 2 oligosaccharides using inhibitory compounds in an organism, and further whereby treatment effects are provided inflammation, and since determination of these factors (e.g. the targeting and inhibition of core 2 GlcNAc transferase using inhibitory compounds) is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

*Related Prior Art*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

King et al USPN 6,131,578 teaches increased expression of core 2 GlcNAc transferase expression in cardiomyocytes harvested from spontaneous autoimmune-caused diabetic nonobese diabetic (NOD) mice. King is distinguishable from the instant invention because King teaches the increased expression of core 2 GlcNAc transferase activity in cardiomyocytes, but does not provide any in vitro or in vivo inhibition of transferase activity using inhibitory molecules. King teaches a correlation between increased transferase expression under diabetic conditions in a mouse model, and teaches the in vitro transfection of recombinant core 2 GlcNAc transferase in Cos cells.

***Conclusion***

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

*JZ*
5-24-04

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600